clophosphamide 300 mg/m^2 IV d3–6, Fluorouracil 400 mg/m^2 IV d3–6, every 28 days) improves survival of N+ breast cancer (BC) patients (pts). In 1981, Tamoxifen (TAM) had recently been shown to increase the expression of the Progesterone Receptor in breast cancer cell lines. This notion, together with the idea that chemo-hormonotherapy might surpass chemotherapy alone in Hormonal Receptor-positive (HR+) BC pts, was the basis of the present randomized phase III trial, conducted between 1981 and 1985 in 6 french cancer centers.

Patients and Methods: 238 pts bearing HR+ Node-positive (N+) BC were randomized to either monthly AVCF for 6 courses (n = 134), or the same plus an alternance of oral Tamoxifen, 30 mg daily for 14 days, and oral Medroxyprogesterone Acetate, 500 mg daily for 14 days (AVCF-TM), during one year (n = 104). Median age was 53 years. 54% of the pts were postmenopausal. 46% also received locoregional radiation therapy. Most tumors were T1 or T2 (84%). SBR histoprognostic grades, determined in 70% of the pts, were as follows: grade 1, 26%; grade 2, 62%, Grade 3, 12%. Two thirds of the pts had ^{2} 3 nodes involved. Major prognostic factors were well-balanced between both arms.

Results: 236 pts are available for final analysis. Although grade 3 to 4 acute toxicities were rare, one toxic death occurred, due to febrile neutropenia. At a median follow-up of 12.9 years (1–15), no difference could be detected between the two treatment arms in terms of Disease-Free Survival (50 vs 51%, p = 0.91) nor Overall Survival (OS) (53 vs 54%, p = 0.86). We also failed to elicit a benefit for pts over 60 years, as it had been previously described. A significant advantage in OS was noticed for the AVCF-TM arm in the SBR grade 3 subgroup of pts (p = 0.006), but the samples, although well balanced, were very small (8 and 10 pts). The incidence of contralateral breast cancer (CBC) was not different between both groups (10-year cumulative incidence 5.5 and 6.5%). However, interestingly, the median Time-To-CBC was much longer in the AVCF-TM arm: 112 (45.6–149) versus 61 (12–104) months.

In conclusion, this is the first report of the use of an alternated hormonal therapy in the adjuvant treatment of breast cancer. However, this short-duration hormonal therapy failed to add any benefit to an adjuvant anthracyclin-based chemotherapy regimen (AVCF) in HR+ N+ pts.

P105 Inhibition of Tamoxifen's therapeutic benefit by Tangeretin in mammary cancer

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Overall survival for patients with primary breast cancer is increased by adjuvant therapy with Tamoxifen. Resistance to Tamoxifen is one of the reasons for treatment failure in mammary cancer patients. Flavonoids from the diet have been implicated in this problem through direct estrogenic effects on the tumor cells or induction of Tamoxifen's liver metabolisation. Tangeretin, a citrus flavonoid with extensively studied effects on human mammary cancer cells *in vitro*, was tested in combination with Tamoxifen in tumor-bearing laboratory mice. Our model consisted of estrogen-primed female nude mice inoculated subcutaneously with human MCF-7/6 mammary carcinoma cells. Oral treatment of the mice with Tamoxifen inhibited the growth of the MCF-7/6 tumors as compared to solvent controls ($p < 0.001$ in Student's *t*-test). Tangeretin, added to the drinking water with Tamoxifen, completely neutralized the effect of Tamoxifen. Furthermore, Tamoxifen/Tangeretin treatment reduced the median survival time of the tumor-bearing mice as compared to the Tamoxifen-treated group (14 versus 56 weeks; p = 0.002 in Mantel-Cox Logrank test). Remarkably, the growth-inhibiting effect of Tamoxifen could be reversed upon addition of Tangeretin to the drinking water: tumor growth resumed after a median lag period of 14 weeks.

Induction of liver metabolisation of Tamoxifen by Tangeretin was ruled out. Tamoxifen concentration was not lower in tumor and tissues from Tamoxifen/Tangeretin treated mice than from Tamoxifen treated ones.

Taken together, our results plead against excessive consumption of Tangeretin-containing citrus products during the Tamoxifen treatment of mammary cancer.

P106 A lack of evidence for the genotoxicity of tamoxifen and toremifene in the human endometrium

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The association of the drug tamoxifen with human endometrial cancer has been the cause of considerable controversy. Debate has centred upon whether tamoxifen is genotoxic to human tissues, as is the case in the rat where it is metabolised to a reactive intermediate which gives rise to high levels of DNA adducts in the liver (a genotoxic event). A study exploring DNA adduct formation in human endometria, utilising Thin Layer Chromatography-^{32}P-postlabelling, found no evidence for such adducts in women treated with the drug [Carmichael *et al.* 1996 *Cancer Res.* 56 1475–9]. However, a subsequent study utilising High Performance Liquid Chromatography (HPLC)-^{32}P-postlabelling suggested that very low levels of adducts could be detected in 5 out of 7 endometrial samples from 6 patients treated with 20 or 40 mg/day tamoxifen [Hemminki *et al.* 1996 *Cancer Res.* 56 4374–7]. Through a joint-centre approach, we have sought to confirm or dispute these findings by reproducing the HPLC methodology at both Imperial College and the Institute of Cancer Research, analysing endometrial DNA from 20 patients treated with 20 mg/day tamoxifen for a period of between 22 and 65 months. We have found no evidence for the presence of tamoxifen-derived DNA adducts in any of these tissues as compared to rat adduct standards, and furthermore found no evidence for DNA adducts induced by the tamoxifen analogue, toremifene in endometria from 8 patients treated with 60 mg/day for 6 or 12 months. On the basis of this evidence and previous studies, we suggest that neither tamoxifen nor toremifene are metabolised in women to electrophiles that bind DNA in sufficient quantity to be genotoxic or carcinogenic. However, we cannot rule out the possibility that tamoxifen may modulate levels of endogenous DNA adducts or have other effects on human endometrial tissue.

P107 The 'ZEBRA' study: 'Zoladex' (goserelin) vs CMF as adjuvant therapy in the management of node positive stage II breast cancer in pre/peri-menopausal women aged 50 years or less

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'Zoladex' (goserelin) suppresses ovarian function and is an established and effective endocrine therapy for the management of advanced breast cancer in pre/perimenopausal women, convenient to administer and well tolerated. The exact role of goserelin as an adjuvant treatment for early breast cancer in pre/peri-menopausal women remains to be defined. The ZEBRA ('Zoladex' Early Breast Cancer Research Association) study was set up to evaluate goserelin in a comparative study against cytotoxic chemotherapy, the current systemic adjuvant treatment most often used in this age group.

The ZEBRA study was started in 1990 as a collaboration between Zeneca (formerly ICI) Pharmaceuticals, the German Breast Cancer Group and the University of Freiberg. ZEBRA is an open randomised clinical trial comparing goserelin (2 years therapy of one 3.6 mg depot injection every 28 days) with the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (6 × 1 monthly cycles) in the management of node positive stage II breast cancer in pre/peri-menopausal women aged ≤50 years. Recruitment to the study was completed in December 1996 with 1640 patients enrolled. The first analysis is planned for mid-1999.

The objective of the study is to compare disease-free survival (DFS), overall survival, safety and adverse events for the two treatment arms.

Concurrently with the main study there are two additional comparisons between goserelin and CMF. These are: 1) *Bone*, where loss of bone mineral density during and after treatment is being determined in 187 patients. 2) *Quality of Life* in 1466 patients. Also, two further projects are planned: to assess the endocrine status of patients completing two years therapy with goserelin and to determine oestrogen receptor status for subgroup analyses comparing goserelin and CMF in terms of survival and DFS.

'Zoladex' is a trademark property of Zeneca Limited.

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Friday, February 27, 1998 **9.00–18.00**

Quality of Life, Toxicity

P108 Assessement of changes in life quality of breast cancer patients under adjuvant CMF-chemotherapy by means of the EORTC QLQ-C30

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The Analysis of Life Quality (LQ) is an important parameter in the evaluation of chemotherapy (CHT) nowadays. The European Organization for Research and